COMMON PEDIATRIC DISEASES:
AN UPDATED REVIEW

Editors:
Nima Rezaei
Noosha Samieefar

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Updates on Pediatric Health and Diseases

(*Volume 1*)

Common Pediatric Diseases: an Updated Review

Edited by

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&

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Network of Interdisciplinarity
in Neonates and Infants (NINI),
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Volume # 1

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PREFACE

Seeing the world through the eyes of a child/infant sounds inspirational. They are little, lovely, and defenseless. Pediatric is the science of taking care of these cute creations. Pediatric is a branch of medicine that focuses on the diagnosis and treatment of infants, children, and adolescents' diseases. As the medical sciences are getting more complex with the information explosion, interdisciplinarity is the essential tool to integrate different topics. Therefore, we established an interest group, entitled "Network of Interdisciplinarity in Neonates and Infants (NINI)" in the Universal Scientific Education and Research Network (USERN), and invited pediatricians and scientists in the field of pediatrics from all over the world to join this multidisciplinary network: https://usern.tums.ac.ir/Group/Info/NINI

The "Updates on Pediatric Health and Disease" series is a comprehensive text regarding childhood and adolescence health and diseases. Neonatology, as well as different diseases in all subspecialties of pediatrics, including pediatric allergy and immunology, pediatric cardiology, pediatric endocrinology, pediatric gastroenterology, pediatric hematology, pediatric infectious disease, pediatric nephrology, pediatric oncology, pediatric pulmonology, pediatric rheumatology, pediatric neurology, pediatric psychiatry, and pediatric dermatology, will be discussed in different volumes.

"Common Pediatric Diseases: An Updated Review" is the first volume of this book series; in this volume, after a rapid introduction to Pediatric diseases (Chapter 1), pediatric rheumatologic diseases are discussed (Chapter 2). Then, the book provides an update on common oral diseases (Chapter 3). Chapter 4 takes a specific view of Pediatric Metabolic Syndromes. The book also provides some chapters regarding neurologic diseases, including Pediatric Epilepsy Syndromes (Chapter 5), Pediatric Demyelinating Disorder (Chapter 7), and also a diagnostic algorithmic approach to Pediatric Genetic Epileptic Encephalopathies (Chapter 6). It contains several chapters concerning updates of Henoch-Schönlein purpura (Chapter 9), Atopic Dermatitis (Chapter 8), Childhood-Onset Systemic Lupus Erythematosus (Chapter 10), Severe Combined Immunodeficiency (Chapter 11), PFAPA- Periodic Fever, Aphthous Stomatitis, Pharyngitis, and Cervical Adenitis Syndrome (Chapter 12) and Pediatric Hepatoblastoma (Chapter 13).

Updates on Pediatric Health and Disease Book is the result of the valuable contribution of scientists and clinicians from well-known universities/institutes worldwide. I would like to hereby acknowledge the expertise of all contributors for generously devoting their time and considerable effort in preparing their respective chapters. I would also like to express my gratitude to the Bentham Science publication for providing me the opportunity to publish the book.

Finally, I hope that this timely book will be comprehensible, cogent, and of special value for researchers and clinicians who wish to extend their knowledge of Pediatrics.

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I would like to express my gratitude to the Editorial Assistant of this book, Dr. Noosha Samieefar. Undoubtedly , the book would not have been completed without her contribution.

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DEDICATION

This book would not have been possible without the continuous encouragement by my family.

I wish to dedicate it to my daughters, Ariana and Arnika, with the hope that we learn enough from today to make a brighter future for the next generation.

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CHAPTER 1

Introduction of Common Pediatric Diseases

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Abstract: Pediatric health has improved over the past decades and there is a decline in deaths caused by infectious diseases. Yet, the top three causes of disease in children younger than 10 years in 2019 include neonatal disorders, lower respiratory tract infections, and diarrheal diseases. While in the adolescence age group, the major causes are road injuries, headache disorders, and self-harm. Preterm birth complications, pneumonia, and birth asphyxia are the most leading cause of death in children under five years. While in the five to nine years of age group, injuries, including road traffic injuries, drowning, burns, and falls, are the leading causes of death.

Keywords: Communicable disease, Disease, Epidemiology, Health, Infectious disease, Integrated medicine, Inter-disciplinary, Medicine, Morbidity, Mortality, Multi-disciplinary, Non-Communicable disease, Pediatrics, Pediatrician.

INTRODUCTION

Pediatrics, a branch of clinical medicine that studies the diseases and health conditions associated with infants, children, and adolescents, is not just a profession but solicitude. Children should not be considered tiny adults, and their diseases must be studied and investigated professionally and specifically.

With information explosion and new advances in medical sciences, pediatrics is going to be a set of subspecialties rather than just a specialty.

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This emphasizes the need to develop multidisciplinary and inter-disciplinary approaches and researches. Care coordination could be defined as "a patient- and family-centered, assessment-driven, team-based activity designed to meet the needs of children and youth while enhancing the caregiving capabilities of families. Care coordination addresses interrelated medical, social, developmental, behavioral, educational, and financial needs to achieve optimal health and wellness outcomes". The results of such different disciplines coordination are efficient care coordination, cost efficiency, improvement of the team working, better communication with families, and finally better health outcomes [1].

Particularly, the mental health care of children is a neglected part of primary care settings. The integrated care models in multidisciplinary centers with psychiatric consults would result in better mental health outcomes [2].

Another condition in which integrated approaches are critical is the management of severe cases as they usually suffer from comorbidities simultaneously.

However, these integrated models demand a precise schedule and a well-designed set of collaborations. Additionally, all the medical services should not be directed in highly specialized pediatric centers that would reduce the local hospital referrals [3].

In this chapter, firstly, we review the epidemiology and trend of pediatric diseases. Then, a brief review of common pediatric diseases based on the organ involved is provided.

EPIDEMIOLOGY

The health status of children is improving over the years. The burden of diseases among children under 10 years has declined dramatically about 60 percent, during the years 1990-2019. The reason is better management of infectious diseases, mainly lower respiratory tract infections, diarrheal diseases, and meningitis. However, communicable diseases are still a leading cause of morbidity in children accounting for six of the top ten causes of burden in children. The main causes of disease burden in children younger than 10 years in 2019 include neonatal disorders, lower respiratory tract infections, diarrheal diseases, congenital birth defects, malaria, meningitis, dietary iron deficiency, protein-energy malnutrition, whooping cough, STIs (sexually transmitted infections excluding HIV), respectively.

In the 10-24 years age group, which include adolescents, the top ten causes of burden include road injuries, headache disorders, self-harm, depressive disorders,

interpersonal violence, anxiety disorders, low back pain, dietary iron deficiency, HIV/AIDS, and diarrheal diseases, respectively [4].

The common causes of death among children could be categorized as follows: 1. Respiratory diseases like pneumonia, whooping cough, *etc*. 2. Gastrointestinal diseases like diarrhea, hepatitis, *etc*. 3. Malnutrition and nutritional disorders 4. Malaria 5. Chronic neurological diseases include hydrocephalus, cerebral palsy, and so on 6. Acute neurological diseases such as meningitis, encephalitis, *etc*. 7. Tuberculosis leading to pulmonary, extra-pulmonary, or disseminated involvements 8. Acute rash and fever/infection like Measles, dengue fever, *etc*. 9. HIV infection 10. Emergencies like bowel obstruction, trauma, poisoning, *etc*. 11. Renal diseases include urinary tract infection, acute renal failure, chronic renal failure, *etc*. 12. Endocrine diseases such as diabetes and thyroid diseases 13. Hematological disorders like anemia, bleeding disorders, *etc*. 14. Heart diseases 15. Cancer 16. Child protection problems like sexual and physical abuse, neglect, homicide, suicide, and so on 17. Low birth weight 18. Prematurity 19. Neonatal infections e cord sepsis, congenital infections (examples include syphilis, malaria, rubella), *etc* 20. Perinatal conditions such as birth asphyxia, respiratory distress syndrome, *etc*. 21. Congenital malformations like malrotations, gastroschisis, imperforate anus, *etc* [5].

Preterm birth complications, pneumonia, birth asphyxia, diarrhea, and malaria are reported to be the top five causes of death in children under five years. While in five to nine years of age group injuries, including road traffic injuries, drowning, burns, and falls, are the leading causes of death [6].

According to the United Nations Inter-agency Group for Child Mortality Estimation (UN IGME) report, 6.2 million deaths in children younger than 15 years were recorded only in 2018. Unfortunately, most of these deaths are from preventable causes, and most are in the youngest group, neonates [7].

Although there have been improvements in declining the death rate, there is much to do. The mortality rate has declined from 76 to 39 per 1000 from 2000 to 2018. Many of these deaths occur in sub-Saharan Africa [6].

PEDIATRIC DISEASES TREND

Overall, with increasing Socio-demographic Index or SDI (an index of social development evaluation), pediatric diseases are shifting from communicable to non-communicable [4]. Now, more attention is attracted to psychological and behavioral morbidities and mental health [8].

CHAPTER 2

Updates on Pediatric Rheumatologic Diseases

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Abstract: Rheumatological disorders pose a challenge to clinicians because of multisystemic involvement, relapsing-remitting course, and nonspecific clinical features, which can mimic infections, malignancies, and even genetic disorders. Common symptoms at presentation are joint pain, fever, weight loss, malaise, muscle weakness, rash, and ulcers. While diseases, such as juvenile idiopathic arthritis, juvenile dermatomyositis, and IgA vasculitis, are relatively easy to diagnose because of typical clinical manifestations, others such as systemic lupus erythematosus, scleroderma, and various vasculitides are much more challenging. No laboratory investigation is diagnostic of a particular rheumatological disorder. Investigations, such as antinuclear antibodies and antineutrophilic cytoplasmic antibodies, are associated with a high false-positive rate and should be used judiciously. Most diseases except for Kawasaki disease and IgA vasculitis are chronic and require long-term immunosuppression for control of disease activity. Long-term prognosis has improved over the past few decades due to better immunosuppressive regimens and better monitoring. With an improvement in mortality rates, many children are living into adulthood and facing issues with persistent disease activity and morbidity related to therapeutic regimens. Future research should focus on finding better therapeutic protocols, which should result in further improvements in survival while simultaneously reducing drug toxicity. There is also an urgent need to define better monitoring tools for most rheumatological conditions.

Keywords: ANCA associated vasculitis, Antiphospholipid syndrome, IgA vasculitis, Juvenile dermatomyositis, Juvenile idiopathic arthritis, Juvenile systemic sclerosis, Kawasaki disease, Localized scleroderma, Macrophage activation syndrome, Neonatal lupus, Polyarteritis nodosa, Rheumatological disorders, Systemic lupus erythematosus, Takayasu arteritis, Uveitis, Vasculitis.

RHEUMATOLOGICAL DISEASES IN CHILDREN

Rheumatological diseases pose a real challenge to physicians because of multiple reasons. Signs and symptoms may either be non-specific like fever, weight loss,

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malaise, rash, and joint pains or may point to any organ system in the body. For this reason, these patients may present to any subspecialty of pediatrics. The differential diagnosis in such settings is wide, ranging from infections, inflammatory conditions, malignancies, and sometimes even genetic disorders.

Common manifestations with which patients are brought to pediatric rheumatological services are joint pain, fever, weight loss, malaise, muscle weakness, rash, and ulcers. This chapter will discuss the differential diagnosis of common rheumatological symptoms before discussing specific rheumatological conditions and their management.

When to Suspect Rheumatologic Disorders

Approach to a Child with Joint Pains

Joint pain is the most common symptom of children presenting to pediatric rheumatology services. Physicians need to be able to answer the following three questions after history and physical examination in children presenting with body pains:

1. Whether the pain is articular or not?
2. If articular,
    a. Is the pain inflammatory or non-inflammatory?
3. In case of inflammatory articular pain
    a. Is the involvement acute or chronic?
    b. The pattern of joint involvement: Number of joints involved, symmetry of involvement, peripheral *vs*. axial involvement, small *vs*. large joint involvement, fixed *vs*. migratory *vs*. additive involvement.
    c. Presence or absence of extra-articular features.

These three questions help in the further differential diagnosis. Pediatric gait, arms, legs, and spine (pGALS) test is a useful screening tool for musculoskeletal examination [1]. Though it is not specific to joint disease, it has been shown to improve musculoskeletal examination skills. Detection of any abnormality in pGALS should be followed by a detailed and focused examination of joints and supporting structures.

Whether the Pain is Articular or Not?

Articular pain tends to occur across joint lines, whereas the location of non-articular pain may vary. Articular pain is usually deep, diffuse, occurs along all planes of movement, and occurs on both passive and active movements (Table **1**). Such pain suggests pathology in the synovium, cartilage, and joint capsule.

Table 1. Differences between articular and periarticular pain.

Clinical Feature	Articular Pain	Periarticular Pain
Anatomic structure	Synovium, cartilage, capsule	Tendon, bursa, ligament, muscle, bone
Location of pain	Diffuse, deep	Focal "pin-point"
Pain on movement	Active/passive, in all planes	Active, in a few planes
Swelling	Common	Uncommon; focal if present

On the other hand, periarticular pain is more focal, rather pinpoint, and occurs in few planes. Periarticular pain gets exacerbated with active movements. Such pain is seen due to pathology in tendons, bursa, ligaments, muscles, or bone. Common etiologies are enthesitis, fractures, and osteomyelitis in the metaphyseal region.

Is the Pain Inflammatory or Non-inflammatory?

Inflammatory pain is associated with early morning stiffness and gelling. Early morning stiffness refers to pain and difficulty in moving the joints in the morning on waking up, and it usually tends to last for half an hour or more. Gelling is similar to early morning stiffness but tends to happen after prolonged rest in the daytime. Joint swelling (Fig. **1**) is also indicative of joint inflammation. Redness over the joint is rarely seen except in septic arthritis and reactive arthritis. Warmth and limitation of movement of joints also point to inflammatory causes (Table **2**).

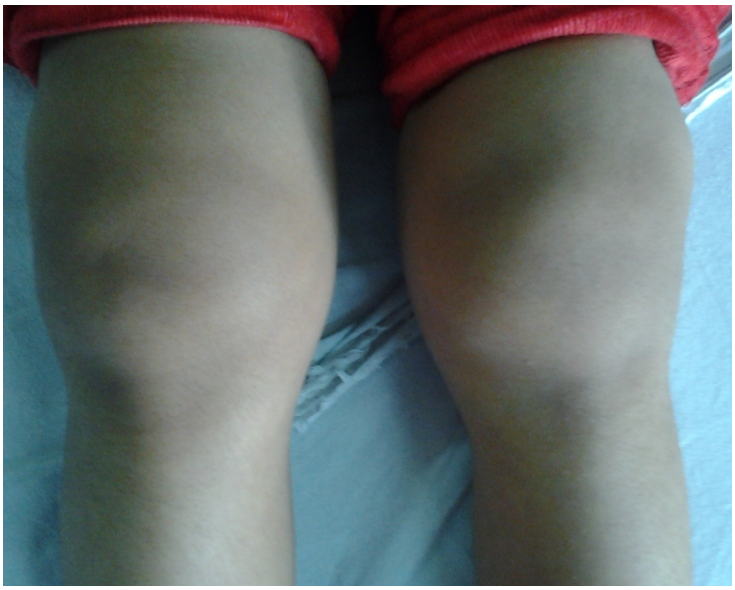

Fig. (1). Joint swelling in both knees suggestive of arthritis.

CHAPTER 3

Updates on Common Oral Diseases in Children

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Abstract: Oral and dental diseases are among the most common problems in children worldwide. If these problems remain untreated, they can have long-term effects on the orofacial system, chewing and speaking abilities, oral health-related quality of life, and overall health status. Dental caries, periodontitis and gingivitis, dental malocclusion, dental trauma, and some oral soft tissue lesions are among the most common oral disorders in children. Early diagnosis and management of these conditions by pediatric dentists and pediatricians necessitate being aware of the clinical manifestations of each disease at every age. Implementing preventive intervention, accurate diagnosis, proper treatment, and performing regular follow-ups are among the key factors for eliminating harmful long-life consequences of poor oral and dental health status in children and adolescents.

Keywords: Aphthous ulcer, Bruxism, Childhood caries, Children, Cyst, Dental caries, Eruption hematoma, Gingivitis, Hemangioma, Infection, Lip biting, Lymphangioma, Malocclusion, Oral habits, Periodontitis, Thumb sucking, Tongue, Tongue thrusting, Tooth, Trauma.

INTRODUCTION

Oral and dental diseases are among the most common problems in children worldwide. If these problems remain untreated, they can have long-term effects on the orofacial system, chewing and speaking abilities, oral health-related quality of life, and overall health status. Pediatric dentists and pediatricians should be aware of the signs and symptoms of these oral conditions for accurate diagnosis from the early steps and proper management to prevent further harmful consequences in the overall health status.

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DENTAL CARIES

Dental caries is the most common chronic infection among children worldwide; *Streptococcus mutans* bacteria are considered the main etiological factor for this common oral disease [1]. According to the World Health Organization (WHO), in 2020, more than 530 million children suffer from dental caries of deciduous teeth; also, permanent teeth dental caries are the most common health issue based on a global assessment of 354 diseases in 2017 [2]. The DMFT index indicates the number of permanent teeth decayed, missing, and filled teeth, which is used as a global index for evaluating dental caries conditions worldwide. Due to the fact that this major public health issue is completely preventable, public health policymakers paid significant attention to implementing strategies to prevent this disease from childhood [3].

Early Childhood Caries (ECC) is one of the major public health problems worldwide; its prevalence is 12-27% among 2 to 3-year-old children, and it reaches 48% in up to 6 years old children. ECC is defined as “the presence of one or more decayed (non-cavitated or cavitated lesions), missing (due to caries), or filled tooth surfaces in any primary tooth in a child under the age of six” [4, 5]. This early onset disease can have major long-term consequences during the lifetime, such as premature teeth loss, future orthodontic problems, speech difficulties, masticatory and chewing issues, higher risk of further carious lesions in permanent teeth, impact on the development and eruption of permanent dentition, and orofacial dysfunction [6]. Thus, it has become one of the priorities of planning preventive interventions among public health managers.

ECC has multifactorial etiology, such as socio-economic status, dietary factors, behavioral problems, and genetic factors [4]; however, inadequate dental plaque removal of the primary teeth in addition to a sugary diet leads to accelerating this process [7]. One of the most prevalent examples of a sugary diet is prolonged usage of baby bottles with sugary contents, especially during the sleep period [4]. Based on a systematic review and meta-analysis, ECC's most important risk factors in high-income families were frequent sweetened meals, improper oral health care, and visible plaque in the oral cavity [8].

However, ECC can involve all primary teeth; it usually involves maxillary incisors (compared to mandibular incisors), followed by molars and canines, consequently (Figs. **1**, **2A**, **2B** and **3**) [9]. One of the most significant characteristics of ECC is the rapid progression of initial white spot lesions in the gingival margin to cavitated lesions in the labial or lingual surfaces of the primary teeth, which is not common in the routine form of tooth decay at this age [4, 9].

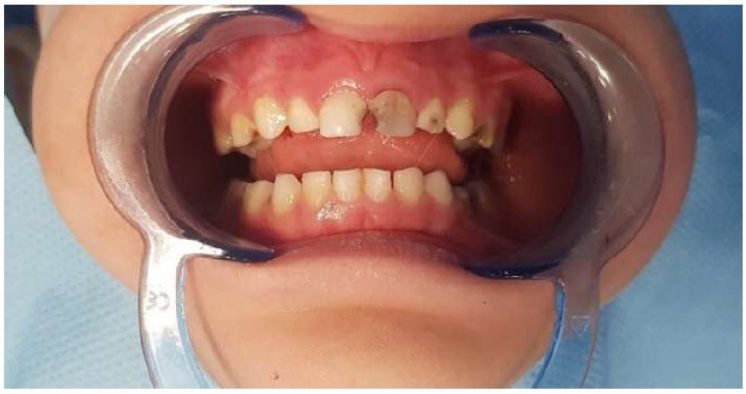

Fig. (1). ECC involving anterior maxillary incisors in a 5-years-old male child.

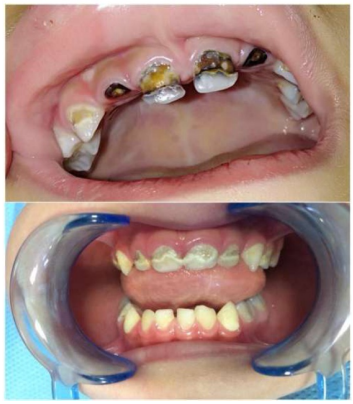

Fig. (2). A.ECC involving almost all primary teeth of 3-years-old children. The central and lateral primary incisors have severe tooth caries leading to complete disruption of the lateral crowns. **B.**ECC in the anterior maxillary incisors in a 4-years-old female patient.

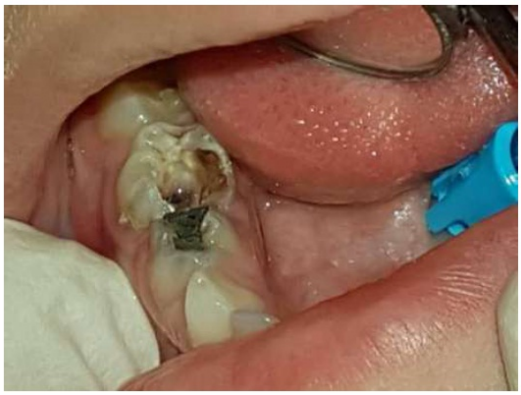

Fig. (3). Cavitated untreated tooth caries in the second primary molar of a 6-years-old child.

CHAPTER 4

Updates on Pediatric Metabolic Syndrome

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Abstract: Metabolic Syndrome (MetS) is considered as the presence of clustering metabolic risk factors. It is rapidly increasing in children and adolescents, notably in low- and middle-income countries. It results from a complex interaction of lifestyle, environmental, and genetic factors. Although its universal definition needs to be determined in the pediatric age group, the main components are obesity, dyslipidemia in terms of elevated triglycerides, and elevated blood pressure. Respectively, fatness and fitness have a direct and inverse association with the development of MetS. Various metabolic responses that are involved in the adipose tissue promote a link between obesity, insulin resistance, inflammation, and future atherogenesis. Management of pediatric MetS would need multidisciplinary interventions, including a multicomponent approach, consisting of healthy eating, reducing screen time, increasing physical activity, as well as providing appropriate duration and quality of sleep. Limiting the exposure of pregnant mothers as well as children and adolescents with endocrine disrupting chemicals is beneficial for preventing the development of MetS. Lifestyle modification and family-centered interventions are the first-line approaches in the treatment of MetS, and the use of medication should be considered only for those who fail to reach healthy weight after lifestyle intervention and for those with underlying disease and complications. Prevention and early management of pediatric MetS are of main strategies for primordial/primary prevention of non communicable diseases.

Keywords: Children and adolescents, Environment, Epigenetics, Lifestyle, Metabolic syndrome, Prevention.

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INTRODUCTION

Metabolic Syndrome (MetS) is characterized as clustering of cardiometabolic risk factors. Although there is no uniform agreement regarding the diagnostic criteria for MetS among children and adolescents, most of the available definitions agree that hypertension, glucose intolerance, central obesity, and dyslipidemia should be included as the main components [1, 2]. In this context, obesity plays a central role, as it represents the main risk for developing metabolic alterations [3].

The prevalence of MetS has increased in the paediatric population in recent years as a result of improper lifestyle habits along with the development of early risk factors [4, 5]. Healthy behaviors, such as regular physical activity practice, healthy diet, adequate sleep patterns, as well as an active routine must be incorporated at an early age, once they are closely related to the development of metabolic complications [6, 7]. In addition, prenatal and postnatal environmental factors, including birth weight, obesity during pregnancy, gestational diabetes, as well as breastfeeding duration, have been considered relevant aspects for the onset of obesity and MetS [8 - 10].

Pediatric MetS is a predictor of this condition in adulthood [11], highlighting the need for the early management of this disease. As the first-line approach, the treatment includes interventions to promote adequate nutrition and physical activity practice, in which multicomponent interventions are the most effective [12, 13]. If this strategy does not result in beneficial effects, pharmacological treatment can be incorporated [14].

Therefore, MetS is a complex disorder that develops at an early age, necessitating the implementation of public health policies to prevent and treat it.Taking these aspects into consideration, this chapter aims to approach the factors associated with MetS development, prevention, and treatment in the pediatric age group.

DEFINITION AND PREVALENCE

MetS is recognized as an important health risk in children and adolescents [15]. It is characterized by a clustering of metabolic abnormalities that result in increased risk for the development of chronic diseases, mainly cardiovascular disease and type II diabetes [16]. In the pediatric age group, studies are proposing a set of different criteria to define MetS, and although there is no consensus among them, the diagnosis criteria agree that some essential components are present, such as glucose intolerance, central obesity, hypertension, and dyslipidemia [1, 17, 18].

In the absence of definitive definitions, adult criteria have been adapted to be applied in the field of pediatrics, and one of the most commonly used is the one

proposed by the International Diabetes Federation (IDF) [1]. According to this group, the parameter required for the MetS diagnosis is the presence of three or more of the following criteria: waist circumference ≥90th percentile, systolic blood pressure ≥130 mmHg; diastolic blood pressure ≥85 mmHg; triglycerides ≥1.69 mmol/L; high-density lipoprotein cholesterol (HDL-C) ≤1.03 mmol/L; fasting glucose ≥5.55 mmol/L. Another widely used definition is the one adapted from the Adult Treatment Panel III (ATP III) [2], in which MetS is defined by the presence of three or more of the following components: waist circumference ≥90th percentile for age and gender; elevated systolic and/or diastolic blood pressure ≥90th percentile for age, sex, and height; triglycerides ≥1.24 mmol/L; HDL ≤1.03 mmol/L; impaired fasting glucose ≥5.6 mmol/L. Although these definitions included the same components, they considered different cut-points for elevated blood pressure and hypertriglyceridemia. Also, the IDF criteria are suitable only for children 10 years or older, while the ATP III can be used for children below the age of 10 years.

There are important limitations attributed to these traditional criteria. Using a binary classification, it is only possible to determine the presence or the absence of the risk factor, which can lead to a lack of durability in the classification, mainly considering the individuals near the limit of individual cut-offs. The instability in the categorical diagnosis of MetS has been shown in studies developed with children and adolescents [19, 20]. Another limitation concerns the disregard of the influence of sex and ethnicity [21].

To overcome these barriers, it has been suggested that the components of MetS should be considered as continuous variables [22, 23]. Thus, several studies have proposed a continuous score to represent the clustering of MetS components, which is justified by the notion that this approach could be less error susceptible compared to the dichotomic one [24]. Additionally, it would provide full information on the health status and is more reliable in predicting young adult cardiovascular risk from childhood [25].

In addition to the traditional elements, some researchers have proposed that other components should be included in MetS diagnosis. According to Andersen *et al*. (2015), the inclusion of cardiorespiratory fitness and leptin could improve the diagnostic criteria. Furthermore, the consideration of non-alcoholic fatty liver disease, hyperuricemia, leptin/adiponectin ratio, and sleep disturbances have also been argued once are related to risks for metabolic impairment [15, 26].

The lack of a universal definition and the different characteristics between populations result in the varying MetS prevalence. A study developed with Chinese schoolchildren compared two definitions and showed that the prevalence

CHAPTER 5

Updates on Pediatric Epilepsy Syndromes

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Abstract: This chapter examines the basics of pediatric epilepsy syndromes and the new factors in the field that lead to and result from the disturbed function. Some disorders such as febrile seizures and idiopathic seizure disorders are fairly common in children, and pediatricians should be familiar with the approaches used to investigate such disorders. However, others, such as rare genetic diseases, are increasing in incidence due to the recent advances in genetic testing and personalized medicine. Nevertheless, epilepsy syndromes carry significant morbidity and even mortality in children. The advent of new genetic discoveries has also brought forth new lines of management for previously refractory diseases. The truly intractable epilepsy syndromes might be managed with surgery as a final resort.

Keywords: Absence seizures, Aura, Childhood epilepsy, Developmental delay, Dravet syndrome, Electrolyte disturbance, Encephalitis, Epilepsy neurosurgery, Febrile seizures, Generalized seizures, Genetic epilepsy, Metabolic epilepsy, Movement disorders, Non-epileptic seizures, Neurological evaluation, Partial seizures, Seizures syndromes, Seizures investigations, Seizures management, Status epilepticus.

INTRODUCTION

Diagnosing seizures is a challenge and should be considered with diligence, as in most cases, it confers a lifelong treatment and, in some cultures, is considered a stigma. A thorough and detailed medical history is paramount for the diagnosis of seizures and is the first step towards a detailed neurological assessment. Thus, history is the first step towards diagnosing pediatric movement disorders along

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with physical examination that guides the clinicians towards a diagnostic approach and eventually the formulation of a management plan.

The history should provide a chronological timeline to the chief complaint, focusing on signs and symptoms associated with the suspected seizure, duration of the episode, any possible post-seizure symptoms, events leading to the episode, and any alleviating or aggravating elements. Whenever possible, clinicians should seek video recording of alleged episodes to further look into the condition, as even a short film would carry more information for the trained eyes than a lengthy description by a parent or a caregiver [1].

An integral part of the complete history of newly onset seizures is a review of systems, specifically looking for; 1) history of other symptoms that might be misattributed to other systems (*e.g*., vomiting, fatigue, aura), 2) systemic illness that might lead to central nervous system manifestations (*e.g*., lupus, metabolic diseases, mitochondrial disorders), 3) Possible infectious etiologies (*e.g*., rheumatic fever, respiratory infections, urinary tract infections), 4) possible toxins exposure/poisoning (*e.g*., lead exposure, pesticide exposure, neuropsychiatric medications ingestion). Auras can present in different formats, including 1) visual (color changes, flashing lights, seeing floaters and visual hallucinations), 2) tactile, 3) auditory, 4) olfactory, 5) others (*e.g*., déjà vu, vestibular changes)

Detailed birth history must be obtained; this will further elucidate any risk of perinatal acquired conditions. This part starts with history prior to conception and follows till the end of the neonatal period. Clinicians should ask specifically about common pregnancy-related complications, including 1) adequate supplements intake during pregnancy, 2) perinatal follow up (and whether any concerns were raised about pregnancy-induced hypertension, preeclampsia, gestational diabetes, and infections), 3) gestational age at delivery and mode of delivery, 4) admission to neonatal intensive care and the reasons (if any), 5) quantify drug intake during pregnancy (including alcohol, prescription and illicit drugs, smoking, and any herbal remedies usage during pregnancy), 6) nature of fetal movement during pregnancy, 7) birth parameters (weight, length, and head circumference) should be noted, 8) if the patient had developed neonatal jaundice (in such case the clinician should inquire about the highest recorded level of bilirubin and mode of treatment), and 9) newborn screening results can also provide clues to neurological manifestations of metabolic disease. Obtaining medical records of patients might provide further insight into past medical history and possible etiologies for newly onset seizures [2].

A developmental history is an important tool in the diagnostic approach to newly onset seizures, especially if there are concerns about delay in acquiring skills or, more ominously, if a patient has lost skills. The knowledge about the range of time to skill acquisition and mastery are indispensable tools to correct diagnosis of newly onset seizures. Table **1** summarizes developmental milestones for the first 2 years.

Table 1. Expected developmental milestones and age of acquisition in the first two years of life.

Age	Gross Motor	Fine Motor	Speech / Language	Cognitive / Problem Solving	Social / Emotional
Newborn	Primitive reflexes – steps, place, Moro, Babinski, ATNR, Flexor posture	Primitive reflexes – grasp	Primitive reflexes – root, suck Alerts to sound Startles to loud sounds Variable cries	Visual focal length – 10 degrees Fix and follow slow horizontal arc Prefers contrast, colours, face Prefers high pitched voice	Bonding (parent -> child) Self-regulation/soothing
2 months	Head steady when held Head up 45 degrees prone	Hands open half of the time Bats at objects	Turns to voice Cooing	Prefers usual caregiver Attends to moderate novelty Follows past midline	Attachment (child -> parent) Social smile
4 months	Sits with support Head up 90 degrees prone, arms out Rolls front -> back	Palmar grasp Reaches and obtains items Brings object to the midline	Laugh, razz, “ga”, squeal	Anticipates routines Purposeful sensory exploration of objects (eyes, hands, mouths)	Turn-taking conversations Explores parent's face
6 months	Postural reflexes Sits tripod Rolls both ways	Raking grasp Transfers hand to hand	Babbles (nonspecific)	Stranger anxiety Looks for dropped or partially hidden object	Expresses emotions: happy, sad, mad Memory lasts – 24 hours

CHAPTER 6

Updates on Pediatric Genetic Epileptic Encephalopathies: A Diagnostic Algorithmic Approach

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Abstract: Epileptic Encephalopathies (EEs) are a heterogeneous group of epilepsy syndromes predominantly seen in neonatal, infantile, and childhood age groups. EEs present with varied signs and symptoms often pose a diagnostic dilemma for the treating physician. The diagnostic complexities imposed by variable age of presentation and overlapping clinical signs and symptoms in EEs are further increased by exhaustive new information from advanced molecular genetic techniques like next-generation sequencing. Taking into account all these challenges, the main objective of this chapter is to briefly outline important diagnostic signs and symptoms, EEG, imaging and genetic findings of common neonatal, infantile and childhood-onset genetic epileptic encephalopathies, and secondly, to draw a simple and pragmatic diagnostic algorithm for the diagnosis of genetic epileptic encephalopathies by the treating physicians. Systematic diagnostic algorithms of commonly occurring EEs would not only guide physicians regarding the management of the patients but also help to counsel parents regarding the prognosis, risk of inheritance, and prenatal testing.

Keywords: Algorithm, Diagnostic, Dravet, Drug-resistant, Epileptic, Encephalopathies, Febrile, Genetics, Infantile, Landau-Kleffner, Lennox-Gastaut, Molecular, Myoclonic, Neonatal, Ohtahara, Pediatric, Semiology, Syndrome, Treatment, West-syndrome.

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INTRODUCTION

Seizures in childhood are one of the commonest neurological symptoms encountered in clinical practice, and they range from a benign single seizure episode to intractable epilepsy and encephalopathy [1]. Epileptic encephalopathies (EEs) are devastating conditions characterized by drug-resistant generalized or focal seizures, electroencephalographic (EEG) abnormalities, and impaired cognitive, sensory, and motor development. It is reported that 40% of all seizures during first three years of age are due to EEs. The majority of children with EEs become resistant to available antiepileptic drugs (AEDs) and are prone to premature deaths, injuries, and poor quality of life. The underlying etiologies of EEs remain heterogeneous, ranging from idiopathic to potentially morbid genetic variants.

It has been found in a recent study that a genetic cause could be attributed in 28% of the children with EEs based on the diagnostic genetic testing [2], highlighting the complexity involved in making the diagnoses of EEs. Early diagnosis and therapeutic interventions are vital as these can alter the course of the disease and improve the final outcome. Considering a significant overlap and complexity among signs and symptoms seen in children with EEs and the difficulties associated with making an early diagnosis of EE, the main objectives of this chapter are a) to briefly outline important signs and symptoms, EEG, imaging, and genetic findings of common neonatal, infantile and childhood genetic epileptic encephalopathies, and b) to draw a simple and pragmatic algorithm for the diagnosis of genetic epileptic encephalopathies.

NEONATAL EPILEPTIC ENCEPHALOPATHIES

Neonatal Epileptic Encephalopathies (NEE) is an autosomal dominant, severe form of encephalopathy where seizures start as early as the first week of life [3]. Infants predominantly develop tonic seizures with associated autonomic features that remain recurrent and refractory to conventional antiepileptic medications. Sodium channel blockers like carbamazepine and phenytoin have shown some benefits and are considered first-line treatment. Ictal EEG typically shows a burst suppression pattern or multifocal epileptiform activity. Brain imaging shows hyperintensities in bilateral basal ganglia and thalamus that usually resolve by the age of three. Seizure cessation occurs anytime between nine months to four years of age but ensues a lasting neurological sequel with moderate to severe developmental delay in all domains [4]. EEG usually becomes normal with control in seizures [5]. *KCNQ2* (voltage-gated potassium channel) is implicated in this disorder harboring a heterozygous missense pathogenic mutation.

Another EE subtype, Benign Familial Neonatal Epilepsies (BFNE), is a rare form of epilepsy presenting in the early neonatal period. The onset is typically between the second to the eighth day of life. These infants develop brief but sometimes recurrent seizures that include tonic or apneic seizures, focal clonic activity, and autonomic symptoms. They are amenable to conventional antiepileptic medications and leave no neurological sequel. All laboratory investigations, including brain imaging, are normal [6]. Ictal EEG shows focal discharges that may secondarily generalize. Inter-ictal EEG is usually normal, rarely it shows 'theta pointu alternant' activity, characterized by dominant theta activity, non-reactive, inter-hemispheric asynchrony, and sharp waves. BFNE is autosomal dominant genetic epilepsy with mutations in *KCNQ2*, coding for a subunit of the voltage-gated potassium channel in the brain [7]. A heterozygous pathogenic variant (60-80% cases) [8] or deletion/duplication (20-40% cases) [9] in *KCNQ2* can cause the disease with a penetrance of 77-85% [5]. A minority of infants with BFNE harbored mutations in *KCNQ3,* a close homolog of *KCNQ2,* and one family harbored pericentric inversion of chromosome 5 [10]. BFNE has a good prognosis with spontaneous resolution of seizures by twelve months of age with no lasting sequel.

Ohtahara Syndrome

The seizure onset is specifically in the neonatal or early infantile period. The majority of seizures are present in the first month of life with recurrent episodes of tonic spasms, sometimes in clusters. There can also be associated generalized seizures, hemiconvulsions, and focal seizures but tonic spasms are more consistently observed in Ohtahara syndrome. Interestingly, myoclonic epilepsy has not been associated with Ohtahara syndrome [11]. The seizures can be similar to West syndrome (see below), but the age at onset, occurrence of seizures in both awake and sleep states, and specific EEG changes, differentiate it from West syndrome [12]. Clinically, Ohtahara syndrome is characterized by daily, recurrent seizures, with significant psychomotor delay and a poor prognosis. The characteristic EEG abnormality is the suppression burst pattern with sudden high voltage bursts alternating with flat records denoting the suppression. These alternations occur periodically in both awake and sleep states, differentiating it from West syndrome, which shows remarkable periodicity in sleep. The most common underlying pathology has been structural brain abnormalities like cerebral dysgenesis and cortical malformations. Ohtahara syndrome in a majority of cases progresses to West syndrome, as reported by a longitudinal study [13]. Ohtahara syndrome has poor prognosis with intractable seizures and significant psychomotor delay. Treatment trials with ACTH injections, clonazepam, ketogenic diet, and vitamin B6 supplementation have not shown any significant benefit [14].

CHAPTER 7

Updates on Pediatric Demyelinating Disorders

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Abstract: Myelin is a protective layer that enwraps the axonal terminals and is an essential component of the central nervous system white matter. Loss of myelin leads to conduction block in the axon leading to demyelinating disorders. Inherited poor formation of myelin is known as *hypomyelination,* and abnormally formed myelin is called *dysmyelination*. Demyelinating disorders exclude diseases where degeneration of the axon is the initial event and myelin is degraded secondarily. Most neurologists use the term *demyelination only for* acquired forms of loss of myelin with relative preservations of axons due to inflammation such as multiple sclerosis. Demyelinating disease in children may be monophasic (*e.g*., acute disseminated encephalomyelitis, optic neuritis, and transverse myelitis) or chronic (multiple sclerosis and neuromyelitis optica). Pediatric multiple sclerosis is the most common demyelinating disorder in children. Recent genetic and clinical researches have significantly improved our understanding of the diverse spectrum of pediatric demyelinating disorders. In this chapter, an updated summary of the current knowledge on the categories, diagnosis, as well as management of pediatric demyelinating disorders has been presented.

Keywords: Adolescent, Central Nervous System/immunology, Central Nervous System/pathology, Child, Demyelinating Diseases/diagnosis, Demyelinating Diseases/drug therapy, Demyelinating Diseases/immunology, Demyelinating Diseases/pathology, Encephalomyelitis, Acute Disseminated / cerebrospinal fluid, Encephalomyelitis, Acute Disseminated/diagnosis, Humans, Magnetic Resonance Imaging, Multiple Sclerosis/cerebrospinal fluid, Multiple Sclerosis/diagnosis, Multiple Sclerosis/drug therapy, Myelin-Oligodendrocyte Glycoprotein / immunology, Neuromyelitis Optica/cerebrospinal fluid, Neuromyelitis Optica/diagnosis, Neuromyelitis Optica/drug therapy, Serologic Tests, Treatment Outcome.

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INTRODUCTION

Axonal terminals, cylindrical processes that arise from the axon hillock of every neuron, have synaptic connections with other neurons. Myelin is a protective layer that enwraps these axonal terminals and is an essential component of the central nervous system (CNS) white matter. Myelin is an extended component of the cell membrane in the nervous system and is divided into segments over the length of specialized nerve fibers. It works as an insulator to prevent loss of action potential current and increases the transmission velocity of stimulus in nerve fibers by decreasing membrane capacitance so that the charges are not able to accumulate at a point. The transmission speed of the action potential is faster in myelinated neurons as compared to unmyelinated ones. Myelin in CNS is produced by oligodendrocytes, and in PNS, it is produced by Schwann cells.

Myelin loss leads to conduction block in the axon by increasing membrane capacitance, accumulation of charges at the point of lost myelin, and slowing down the rate of nerve impulses transmission, thereby results in derangement of the neurologic functions [1]. The absence of myelin may be acquired or inherited. Inherited disorders of poorly formed myelin are known as hypomyelination disorders, and abnormally formed myelin is called dysmyelination [2].

Demyelinating disorders exclude those diseases where degeneration of axon is the initial event and myelin is degraded secondarily [3]. Most neurologists use the term *demyelination only for* acquired forms of myelin loss with relative preservations of axons due to inflammation such as multiple sclerosis [4]. Acquired disorders of demyelination are due to inflammation or immune-mediated destruction of normally formed myelin [5]. Poser also termed this group of myelin disorders as “demyelinating or myelinoclastic diseases” [6]. Acquired disorders of demyelination due to inflammation comprise both the central (CNS) and peripheral nervous system (PNS) myelin disorders. These are rare disorders with an incidence of 0.5-1.66 per 100,000 children per annum [7]. Demyelination is often preceded by an infectious illness, ischemic attack, or maybe due to a metabolic or hereditary defect. The cause of disorders that primarily affect myelin is idiopathic or unknown but may be due to the autoimmune process [8]. The wide spectrum of neurological signs and symptoms are covered by acquired demyelinating disorders due to myelin damage caused by inflammation (Table **1**).

Table 1. Causes of Acquired disorders of CNS demyelination.

Hypoxia and Ischemia	-
Nutritional Deficiencies	Vitamin B12 Deficiency

(Table 1) cont.....

Viral infection of CNS	Progressive multifocal leukoencephalopathy, Subacute sclerosing panencephalitis, Tropical spastic paraparesis/ HTLV-1–associated myelopathy
Primary demyelinating disorders	Monophasic - optic neuritis, acute transverse myelitis, acute disseminated encephalomyelitis Recurrent, progressive disorders – multiple sclerosis, neuromyelitis optica
Toxins and drugs	Alcohol, Carbon monoxide, Ethambutol

CLASSIFICATION OF PEDIATRIC DEMYELINATING DISEASES

Pediatric demyelinating disorders are generally classified as either monophasic (single episode) or polyphasic illness (relapses). In children, most of the demyelinating disorders present with monophasic illness are without any relapse. Monophasic forms of demyelinating disorders in children include acute disseminated encephalomyelitis, transverse myelitis, and optic neuritis. Multiple Sclerosis and neuromyelitis optica spectrum disorder are relapsing or polyphasic forms of demyelinating disorders. On the basis of signs and symptoms' localization, demyelinating disorders can be monofocal if a single lesion can be attributed for manifestations and polyfocal if multiple site lesions are required to explain signs and symptoms [9].

Acute Disseminated Encephalomyelitis

Acute Disseminated Encephalomyelitis (ADEM) is the clinical event of acute inflammatory demyelinating lesions on brain MRI with poly focal neurological deficits in nature and accompanying encephalopathy. ADEM usually presents in early childhood [10 - 12].

Epidemiology

The incidence is 0.1-0.6 per 100,000 per year in children. A study conducted on Canadian children showed an estimated annual incidence of 0.2 per 100,000 [13]. The seasonal pattern of ADEM is seen in North America, with a peak in winter and spring [14, 15]. There is a slight male predominance [16, 17]. The mean age of ADEM presentation is between 5 and 8 years but can occur at any age [18 - 20]. Recurrence is less common as the disease is usually monophasic. The term *multiphasic disseminated encephalomyelitis (MDEM) is used when recurrence occurs after 3 months of the first event.* In ADEM, Myelin oligodendrocyte glycoprotein antibodies (MOG- Ab) are present in the serum of 50% of children [21 - 23]. MOG-Ab antibodies are present in the serum of all cases of MDEM. Multiple Sclerosis (MS) should be suspected if an episode of non- ADEM demyelination affecting a new location occurs after an episode of ADEM and

CHAPTER 8

Updates on Atopic Dermatitis

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Abstract: Atopic dermatitis (AD) or atopic eczema is a complex and multifactorial chronic inflammatory skin disease that is characterized by intense itching and recurrent eczematous lesions. It is very frequent, affecting up to 20% of children in developed countries, and its prevalence has increased worldwide. Patients with AD have an increased risk of developing food allergy, allergic rhinitis, and asthma later in life; but may also present other comorbidities. The main symptom of AD is pruritus, which along with sleep disturbance, decreases the quality of life not only in patients but also in their families. Therapeutic options for AD have historically been limited, but recent advances have increased our understanding of its underlying mechanisms, contributing to the development of new therapies. In this chapter, we review the most recent knowledge about etiology, pathophysiology, clinical manifestations, comorbidities, and treatment options of AD.

Keywords: Atopic Dermatitides, Atopic Dermatitis, Atopic Eczema, Atopic Neurodermatitides, Atopic Neurodermatitis, Disseminated Neurodermatitides, Disseminated Neurodermatitis, Infantile Eczema, Pediatrics, Quality of life.

INTRODUCTION

Atopic dermatitis (AD) -also known as atopic eczema- is a chronic inflammatory skin disease that is characterized by intense itching and recurrent eczematous lesions. AD affects 10 to 20% of children in developed countries, and its prevalence has increased worldwide [1]. Several studies have demonstrated that the presence of AD increases the risk of developing food allergy, allergic rhinitis, and asthma later in life [2, 3]. Comorbidities, pruritus, and sleep disturbance significantly decrease quality of life not only in patients but in their families as well [4]. AD is complex and multifactorial, with historically limited therapeutic options, but significant recent advances have increased our understanding of the underlying mechanisms of AD, contributing to the development of new therapies.

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EPIDEMIOLOGY

There are two main challenges when evaluating the epidemiology of AD: first, there are no widely accepted biomarkers or objective diagnostic tests for AD; and second, there is a lack of standardized nomenclature for AD which makes it difficult to develop consistent questionnaires for epidemiology research [5].

Overall, it is considered that AD affects 10 to 20% of children in developed countries and that its prevalence has increased worldwide in the past 30 years [1, 6, 7]. Prevalence estimates of childhood AD in the United States range from 6% to 12.97%, depending on the study design and approach used [5, 8, 9]. The International Study of Asthma and Allergies in Childhood (ISAAC) is the biggest and only study that has taken a global approach; it provided a global map of AD and found a wide variation in prevalence values worldwide, from 2.0% in Iran to 22.3% in Sweden at ages 6 to 7 years and from 1.4% in China to 21.8% in Morocco at ages 13 years to 14 years [6]. The ISAAC also found a global increase in the prevalence of symptoms of eczema from 1994-1995 to 2002-2003 [6]. Data from the National Health Interview Survey (NHIS), a US population-based household survey, indicates that the prevalence of childhood AD steadily increased from approximately 8% in 1997 to more than 12% in 2010 [5]. Many hypotheses have been explored to explain this increase, including modulation of immune priming by hygiene, gut microbiota diversity, exposure to endotoxins through farm animals, and the effects of pollution, climate, and diet [7].

ETIOLOGY

The pathophysiology of atopic dermatitis is complex and not fully understood yet. It is proposed to be the result of an interaction of genetic and environmental factors that ultimately leads to impaired epidermal barrier function and immune dysregulation (Fig. **1**) [10, 11].

IMPAIRED SKIN BARRIER FUNCTION

The most important function of the skin is to provide an effective barrier between the internal and external environments of an organism. The epidermal barrier limits passive water loss, restricts environmental chemical absorption, and prevents microbial infection. Therefore, any damage to the structure of the skin barrier enhances the penetration of allergens to the skin, increases transepidermal water loss (TEWL), and contributes to immune dysfunction [11, 12].

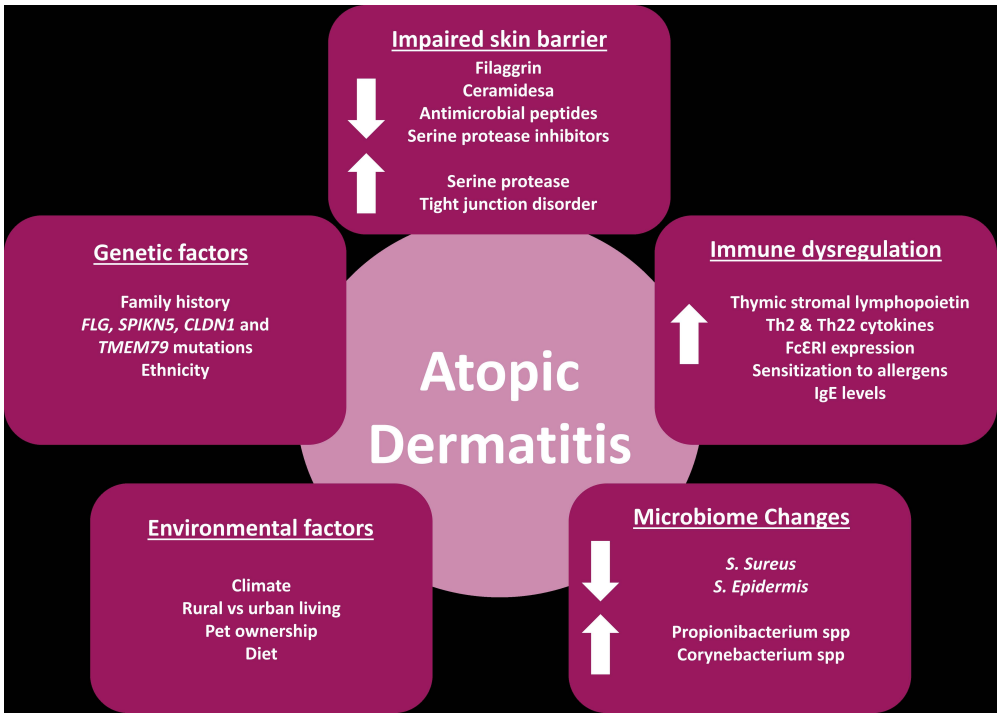

Fig. (1). Skin barrier abnormalities and immune dysfunction are the main features of atopic dermatitis (11).

Major contributors to an impaired skin barrier function include:

Decreased Filaggrin

Filaggrin (FLG) is a structural protein responsible for the keratinization, moisturization, and antimicrobial peptide functions of the skin. It is the main component of keratohyalin granules, and their breakdown products contribute to epidermal hydration and barrier function [13].

FLG can be broken down into free amino acids and converted into urocanic acid, which maintains the acidity level in the skin, and pyrrolidine carboxylic acid, which acts as a natural moisturizer. Mutations in FLG gene are associated with increased TEWL and dry skin in patients with AD [14].

However, 40% of FLG mutation carriers do not develop AD, and FLG mutations are only found in 10% of patients with AD [15]. Therefore, genetic abnormalities in FLG alone do not explain all the skin barrier dysfunctions of AD.

CHAPTER 9

Updates on Henoch-Schonlein Purpura

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Abstract: Henoch-Schönlein purpura (HSP), currently also known as immunoglobulin A (IgA) vasculitis, is the most common vasculitis in children. It is a systemic autoimmune disease mediated by complexes containing abnormal IgA. The cause of HSP is not well known, but the disease is often triggered by an upper respiratory infection in individuals with genetic susceptibility. The diagnosis relies on internationally agreed criteria, including palpable cutaneous purpura of orthostatic location associated with at least one of the following findings: arthralgia/arthritis, gastrointestinal manifestations, leukocytoclastic vasculitis with IgA deposits and/or renal involvement. The skin lesions are essential for the diagnosis. The digestive symptoms, mostly severe abdominal pain, intestinal bleeding, and more rarely, intussusception, maybe the initial and most worrisome clinical component of HSP during the acute presentation of the disease. Nephropathy determines the long-term prognosis. The clinical course of HSP is, in general, favorable. Bed rest results in remission of the purpura that often recurs as the child restarts standing and walking. Corticosteroids are effective, although not usually required, to treat abdominal pain and other severe manifestations. No medical treatment can avoid the possibility of renal involvement that may occur for several months after resolution of the skin lesions. Corticosteroids are used to treat severe forms of HSP nephropathy, which anatomopathologically corresponds to IgA glomerulonephritis. Active research studies are needed to clarify the pathogenesis, the prognostic factors, and the measures to be taken for the prevention and treatment of renal disease.

Keywords: Anaphylactoid purpura, Asialoglycoprotein receptor, ß1,3-galactosyltransferase, Childhood systemic vasculitis, Children, Galactose-deficient IgA1, Henoch-Schönlein purpura, IgA1 isoform, IgA vasculitis, IgA glomerulonephritis, IgAV nephropathy, IgG-Gd-IgA, Immune complexes, Leukocytoclastic vasculitis, Lower limb purpura, Non-granulomatous vasculitis,

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Pediatric purpura, Pediatric vasculitis, Rheumatoid purpura, Small vessel vasculitis.

INTRODUCTION

Systemic vasculitides are characterized by blood vessel inflammation, leading to tissue injury from vascular stenosis, occlusion, aneurysm, and/or rupture. These entities are rare in childhood but are associated with significant morbidity and mortality. Only Henoch-Schönlein purpura (HSP) and Kawasaki disease are relatively common in pediatric patients. HSP is the most common primary systemic vasculitis in children. It is a non-granulomatous form of systemic vasculitis that affects small vessels predominantly.

The term HSP comes from Johann Schönlein and Eduard Henoch, two German doctors who first made a detailed description of the disease in the 1860s [1]. Recent consensus documents have proposed replacing the name HSP with that of IgA vasculitis (IgAV), based on the pathophysiological feature of the disease [2]. Both denominations will be used in this chapter, as the term HSP is widely extended in the medical community and is commonly used in everyday clinical practice. Other nomenclatures such as anaphylactoid purpura and rheumatoid purpura have also been utilized. The association of cutaneous, musculoskeletal, and renal manifestations has led to consider HSP as the cause of the composer Wolfgang Amadeus Mozart's death in 1791, although scientific evidence supporting this hypothesis is missing [3].

According to the internationally accepted classification of vasculitis in childhood [4], the diagnosis of HSP or IgAV includes the mandatory presence of purpura or petechia with lower limb predominance and at least one of the four following criteria: abdominal pain, arthritis or arthralgia, renal involvement (proteinuria, hematuria or red blood cell casts), histopathology findings showing leukocytoclastic vasculitis or glomerulonephritis with predominant IgA deposit.

A detailed description of these criteria will be provided in this chapter. In adults, unlike children, there are no internationally agreed-upon criteria for the diagnosis of IgAV.

EPIDEMIOLOGY

HSP is typical of the pediatric age, although it can also be seen in adults. It is the most common vasculitis among children, the annual incidence having been estimated from 3 to 26.7/100 000 for children and infants and 0.8-1.8/100 000 for adults [5]. The incidence peak stands around 4-6 years, 90% of cases are younger than 10 years of age, and it is rare in infants. HSP is found in both genders with a preponderance of males and in all races, being less frequent in black people with

respect to white and Asian people [6]. There is seasonal variation likely linked to the variable incidence of upper respiratory tract infections [7].

PATHOGENESIS

HSP is a small vessel leukocytoclastic vasculitis of unclear pathogenic origin [8], the combination of genetic susceptibility and environmental risk factors (such as infections, food, vaccination, or drugs) being likely involved in the development of the disease [9].

Around 50% of HSP cases are preceded by an upper respiratory tract infection, suggesting this type of infection is the main trigger of the disease [10, 11], followed by gastrointestinal infections in 5-6% and urinary tract infections in 1%, approximately. Several infectious agents have been implicated, including *group A or B hemolytic Streptococcus, Staphylococcus aureus*, *parainfluenza*, *Helicobacter pylori*, *Parvovirus B19,* or *Epstein-Barr virus*, among others [11]. Some studies found *Streptococcus*, identified by anti-streptolysin (ASO) titer test and throat swab culture, as the most common infectious agent associated with HSP (around 30%) [9]. The relationship between several vaccines and HSP, including influenza A (H1N1) vaccination, has also been described [12].

As for the genetic component, HLA-DRB1*01, HLA-DRB1*11, and HLA-B*41:02 antigens have been proposed to be associated with an increased risk of developing HSP, whereas HLA-DRB1*07 has been conferred a protective effect [9, 13].

HSP is characterized by the deposition of IgA, mainly IgA1 isoform, immune complexes in the vessel walls of dermal capillaries, and in the renal mesangium. IgA-containing immune complexes and high blood levels of IgA in 50% of children can be observed during the acute phase of the illness. In addition, some studies have described the presence of IgA antineutrophil cytoplasmic antibodies (IgA-ANCA), IgA-rheumatoid factor (IgA-RF), or IgA-anti-cardiolipin antibodies (IgA-aCL) [11].

IgA is physiologically present in serum and mucosal secretions. Two IgA isoforms exist, IgA_1 and IgA_2, the former being the most prevalent (90%) in the circulation. In general, IgA_1 has a hinge region containing up to six O-linked glycan chains consisting of N-acetylgalactosamine (GalNAc), sialic acid, and galactose due to ß1,3-galactosyltransferase action [8, 10, 13]. This leads to the clearance of IgA_1 molecules through its interaction with the asialoglycoprotein receptor (ASGP-R) of the hepatocytes [10]. Nevertheless, reduced activity of ß1,3-galactosyltransferase, secondary to genetic predisposition, IL-6 production and/or infections, has been found in HSP patients. Consequently, aberrant

CHAPTER 10

Updates on Childhood-Onset Systemic Lupus Erythematosus

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Abstract: Systemic Lupus Erythematosus (SLE) is a chronic, autoimmune, and multisystem disease. Childhood-onset SLE (cSLE) contributes up to 20% of all cases of SLE and refers to patients who develop the disease before their 18th anniversary.

Impressive discoveries in all aspects of the disease emerge every day; one of the most interesting is whether cSLE is a single or a group of diseases, with diverse physiopathologic processes but sharing a rough phenotype. Patients with early onset disease (<5 years), with associated infections and severe disease manifestations, should urge the possibility of monogenic SLE, which represents a small proportion of all cSLE cases, but often with a more complicated clinical course.

Despite its being considered a rare disease, the clinical outcomes could be devastating. Patients with cSLE had higher disease activity indexes than adults. Although the survival has improved, it also implies that patients remain a longer period under the effects of the disease.

Enormous advances in the understanding of the physiopathological processes are helping to better diagnose children with lupus; still, we are distant to have a perfectly fitted therapy for all our patients. The outstanding efforts of clinicians and researchers to find new therapeutic strategies are encouraging.

In this chapter, you will find a concise description of the novel advancements concerning the disease pathogenesis, classification, assessment of disease activity, treatment, and outcomes.

Keywords: Autoimmune disease, Classification criteria, Childhood-onset, Clinical manifestations, Cyclophosphamide, Disease activity, Damage, Epidemiology, Genetics, Glucocorticoids, Monogenic lupus, Mycophenolate mofetil, Outcome, Pathogenesis, Pediatric, Photoprotection, Systemic lupus erythematosus, Targeted immunotherapy.

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INTRODUCTION

Systemic lupus erythematosus (SLE) is a complex, multisystem, chronic autoimmune disease [1] with the potential to involve any organ or system, with an unpredictable clinical course [2]. Characterized by the presence of numerous autoantibodies [3, 4], it commonly causes organ damage [5].

Childhood onset systemic lupus erythematosus (cSLE) is the preferred term to designate children who before their 18th birthday have met the classification criteria for systemic lupus erythematosus [6]. cSLE represents up to 20% of all patients with SLE [7]; other names as juvenile systemic lupus erythematosus, and pediatric systemic lupus erythematosus, are usually used in the literature.

Since the first cases were reported [8 - 13], impressive and continuous discoveries have been made in all aspects of the disease, one of the most exciting is whether cSLE is one disease or a group of diseases representing groups of patients with different physiopathologic processes, sharing several clinical manifestations and antibody profiles, that as a result, have allowed us to treat them more efficiently. There are many additional interesting aspects of the disease that will be reviewed in this chapter.

EPIDEMIOLOGY

cSLE is considered a rare disease, with higher frequency reported in Asians, African Americans, Hispanics, and Native Americans [14, 15]. The estimated incidence in England was 0.8 (0.5-1.2) per 100,000 children per year, but as mention previously, it varies depending on the ethnic origin. In Asia it was 5.6 (3.0-9.5) and in blacks 3.1 (0.6-9.1) while for whites was 0.4 (0.2-0.7) per 100,000 per year [16]. Australia has reported an annual incidence of 0.32 per 100,000 per year [17]. In the United States of America, the incidence was 2.2 per 100,000 Medicaid enrollees per year, while the prevalence was 9.73 per 100,000 [18]. More recently, an analysis of the online databank of the World Bank Group, taking into account 192 countries in 2017, estimated that there were over 200,000 children with cSLE, the majority concentrated in Asia and Africa, followed by the Americas, Europe, and Oceania with a prevalence of 113,176; 53,731; 24,315; 14,693 and 1,008; respectively [19]. Finally, in Korea, the prevalence was 5.35 per 100,000, and the incidence of 2.2 per 100,000 per year in patients between 5 and 18 years old. Interestingly, the authors noted an increase in the incidence and prevalence of girls age 14 and 15 years, observed in their change-point incidence graphics [20].

The median age at presentation is reported between 11 – 12 years, while the disease is very rare under the age of 5 years [15]. However, there is a tendency to

separate patients by the pubertal stage. Smith and cols [21] resume the findings of Abdwani *et al*. [22], Pluchinotta *et al*. [23], Descloux *et al*. [24], and Gomes *et al*. [25], and the details are depicted in Table **1**.

Table 1. Number of cSLE patients by pubertal stage and gender distribution.

Author	**Age Grouping**			**F:M**
-	**Prepubertal**	**Peripubertal**	**Postpubertal**	**-**
Abdwani, N=103	39	29	35	83:20
Pluchinotta, N=53	13	11	29	38:15
Descloux, N=56	9	21	26	39:17
Gomes, N=847	39	395	413	726:121

There is a clear predominance of girls compared with boys; this tendency seems to increase along with age. In the prepubertal stage, it is about 2 girls for every boy affected (2:1), only Gomes *et al*. reported 4:1. On the peripubertal stage, the sex ratio is more variable, from 2:1 to 6:1, and for the postpubertal stage, it is from 3:1 to 11:1.

The predominance of females in autoimmune diseases, particularly in patients with lupus, does not totally elucidate; however, there is information regarding the role of sex hormones. The estrogen affects all cells of the immune system, resulting in enhancing INF-gamma and antibody production, and together with prolactin, may be implicated in cell survival [26 - 28].

GENETIC AND PATHOGENESIS

Systemic lupus erythematosus is considered a disease resulting from multiple interactions of factors [29]. Familial aggregation is frequent in patients with cSLE [30] who have more relatives with autoimmune diseases, particularly SLE and thyroid disease, than those without lupus [31]. Previous studies in twins indicate a large concordance between monozygotic twins, although it seems that this concordance is lower [32]. Some authors described 15% of SLE heritability. It shows not only the importance of the genetic basis of the disease [33 - 37] but many other factors involved as the epigenetic [38 - 43], ambient, diet, and infections [44 - 46], among many others.

In a recent and comprehensive review of the genetic etiology of SLE, the authors state: "*It was previously thought that the relevant genetic variants and the causal molecular pathway involved in lupus were associated with distinct clinical presentations. This simplification greatly underestimated the biological complexity of this disease. Mutations within the same gene and identical gene*

CHAPTER 11

Updates on Severe Combined Immunodeficiency

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Abstract: Mutations in any one of several genes essential for T lymphocyte development and function cause human Severe Combined Immunodeficiency (SCID), a heterogeneous group of monogenic inborn errors of immunity.

Newborns with SCID acquire multiple, persistent, and severe viral, bacterial, and fungal infections shortly after birth and rarely reach their first birthday. SCID is a pediatric emergency: with prompt diagnosis and treatment, essentially every baby with SCID could be cured by hematopoietic stem cell transplantation or gene therapy.

Most SCID newborns appear normal and healthy at birth, but SCID is always a prenatal disorder of the development of T lymphocytes, and it is already present at birth. Therefore, SCID is detected by newborn screening through measurement of TRECs (T cell receptor excision circles), which counts naïve T lymphocytes, already absent or markedly reduced.

The vast majority of newborns worldwide are not yet screened for SCID. The diagnostic approach and the 'natural history' of affected infants and their families are now completely different depending on whether or not neonatal screening for SCID is available, apart from the availability/unavailability of SCID therapies (hematopoietic stem cell transplantation, *etc*.).

Keywords: B-cell, Bubble boy, Gene therapy, Genetics, Genotype, Hematopoietic stem cell transplantation, Immunodeficiency, Leaky mutation, Lymphopenia, Maternal engraftment, Newborn screening, NK-cell, Null mutation, Omenn syndrome, Phenotype, SCID, T-cell, Thymus, TRECs, Viral vector.

INTRODUCTION

Mutations in any one of several genes essential for T lymphocyte development and function cause human SCID (Severe Combined Immunodeficiency), a heterogeneous group of monogenic inborn errors of immunity with an overall incidence of about 1 in 50,000 to 90,000 newborns [1 - 4]. The incidence is rema-

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rkably higher in many ethnic groups due to the founder effect and common consanguineous marriage (AR, autosomal-recessive, SCID) [5 - 7].

Usually, “null” mutations of these genes with the absence of residual gene/protein function cause Typical SCID, while “non-null” (“hypomorphic”, “leaky”) mutations allowing some residual functions are associated with Atypical SCID.

“Typical/Atypical” refers to the clinical and immunological phenotype, “null/non-null, hypomorphic, leaky” to the molecular findings.

In 2008, Wisconsin, Massachusetts, and the Navajo Nation (USA) became the first states in the world to screen all newborns for SCID by measurement of T cell receptor excision circles, TRECs [8], and as of December 2018, all 50 states in the USA (plus the District of Columbia, Guam and Puerto Rico) performed universal Newborn Screening (NBS) for SCID. Similar NBS have been implemented in Taiwan, Israel, Iceland, New Zealand, Norway, Sweden, Switzerland, Lebanon, Germany, and some regions of Canada, Finland, Spain (Catalonia), Italy (Tuscany). Pilot programs have been completed or are ongoing in Iran, Brazil, Netherlands, Saudi Arabia, UK, France, and other countries [9, 10].

The diagnostic approach to SCID and the ‘natural history’ of SCID infants, their families, and their clinicians are now completely different in these two conditions: NO NBS for SCID *versus* YES NBS for SCID [11, 12].

The vast majority of newborns worldwide are not yet screened for SCID. This happens both in developing countries, where also hematopoietic stem cell transplantation (HSCT) is very rarely available [13], and for example, in most of Europe, where often SCID NBS is absent but, instead, whole-exome sequencing (WES) may be possible.

NO NEWBORN SCREENING FOR SCID

In the absence of NBS, the initial clinical manifestations of SCID are most frequently observed in the first few months of life, and the median age at diagnosis is 4-7 months; so, apart from families with a recognized positive history of SCID (<20 percent of cases), ‘delayed diagnosis, harmful administration of contra-indicated live vaccines, delay in clinical management and poor outcome are still too frequent’ [6].

To achieve a timely clinical/genetic diagnosis, it is essential to know and remember many aspects of SCID [3].

Children with SCID have absent or very low naïve CD3 T cells, do not produce T lymphocytes or, however, functional T lymphocytes, and acquire multiple, persistent and severe viral, bacterial and fungal infections shortly after birth.

Fever, cough, persistent thrush and mucocutaneous candidiasis, upper airway infections, bronchiolitis, pneumonia, skin infections, diarrhoea, meningitis, sepsis, systemic viral infections, disseminated fungal infection, *etc*. affect infants by common and opportunistic pathogens such as cytomegalovirus (CMV), Epstein-Barr virus (EBV), adenovirus, respiratory syncytial virus (RSV), herpes simplex virus (HSV), varicella zoster virus (VZV), rotavirus, norovirus, influenza and parainfluenza viruses, *Staphylococcus spp.*, *Streptococcus spp.*, *Pseudomonas spp.*, *Escherichia coli spp.*, other Gram- *spp.*, *Candida spp.*, *Pneumocystis jirovecii*, *Aspergillus spp.*, *etc* [14, 15].

Children fail to thrive and rarely reach their first birthday.

In SCID (or suspected SCID) infants, it is mandatory that all transfusions involve irradiated and preferably WBC-filtered blood products to avoid the transfusion of functional donor lymphocytes, which would certainly cause life-threatening Graft *versus* Host Disease (GvHD). In fact, this precaution should be used in all newborns as a general rule.

SCID is a pediatric emergency [16] with prompt diagnosis and treatment, and before acquiring an infection, including infections from "live" vaccines, *e.g*., *Bacille Calmette-Guérin* (BCG), or rotavirus [17, 18], essentially every baby with SCID could be cured by HSCT or gene therapy (GT).

Most newborns with SCID appear normal and healthy at birth, but cutaneous signs similar to GvHD from engraftment of transplacentally derived maternal T lymphocytes are sometimes present.

Instead, low birth length and weight, microcephaly, dysmorphic facies, metaphyseal chondrodysplasia or other skeletal abnormalities, alopecia, congenital heart disease, *etc*. are nonimmunological manifestations of the less frequent forms of SCID in which cell types and organs other than lymphocytes and lymphoid organs are also affected by their genetic mutations ("syndromic SCIDs").

However, even if most newborns with SCID appear normal and healthy, SCID is always a prenatal disorder of the development of T lymphocytes, and it is already present at birth.

CHAPTER 12

Updates on PFAPA- Periodic Fever, Aphthous Stomatitis, Pharyngitis, and Cervical Adenitis Syndrome

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Abstract: PFAPA- Periodic Fever, Aphthous Stomatitis, Pharyngitis, and Cervical Adenitis syndrome are the most common autoinflammatory syndromes in children. In this chapter, the characteristic manifestation and clinical criteria of PFAPA, which remain the basis of diagnosis, are presented. The therapeutic options and prognosis are discussed in detail.

Keywords: Adenitis, Anakinra, Aphthous stomatitis, Autoinflammation, Colchicine, Interleukin-1, Interleukin-1 blockers, Marshall syndrome, Periodic fevers, PFAPA, Pharyngitis, Tonsillectomy, Tonsillotomy.

INTRODUCTION

PFAPA syndrome, firstly described in 1987 by Marshall et al., is the most common among the auto-inflammatory diseases of childhood [1, 2]. The name is derived from the first letters of the main clinical symptoms: **P**eriodic **F**ever, **A**phthous stomatitis, **P**haryngitis, and Cervical **A**denitis. Despite the passage of more than 30 years, knowledge about the pathogenesis of the syndrome remains still limited. We currently include PFAPA in the group of autoinflammatory diseases caused by polygenic or complex inheritance of variants in many genes in association with environmental factors. There appears to be no predilection for a particular ethnic or racial group, although male predominance for a particular ethnic group was established [3 - 5]. The concept of auto-inflammation was proposed by Kastner in 1999, and it included genetically determined disorders of

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the innate immune system, manifested by recurrent fever with a different spectrum of accompanying symptoms. Auto-inflammatory diseases, in contrast to autoimmune disorders, are characterized by seemingly unprovoked, pathological activation of the innate immune system in the absence of autoantibodies or autoreactive T cells [6]. This new group of diseases has been dynamically developing in the last two decades and already covers several dozen disease entities, the number of which is systematically growing every year.

ETIOLOGY

PFAPA syndrome has no established genetic basis, may occur sporadically, but quite often, the family history of patients with recurrent fever, tonsillitis, recurrent streptococcal pharyngitis, tonsillectomy, and recurrent aphthous ulcers indicates the possibility of a genetic predisposition, perhaps of a multigenic nature. Although knowledge about PFAPA pathomechanism is still a puzzle, research indicates impaired functioning of the innate immune system. Similarly, as in other classical auto-inflammatory syndromes, the role of inflammasome over-activation and interleukin-1(Il-1) secretion during episodes of fever is underlined. In the course of relapses, IFN-gamma, IFN-gamma induced proteins (IP 10 also called CXCL10 for chemokine, CXC motif, ligand 10) and proteins induced by gamma interferon (MIG or CXCL9), G-CSF, TNF-alpha, and other proinflammatory cytokines (IL-1 beta, IL-6, IL-18) are elevated [7, 8]. Monocytes isolated from patients during fever secrete greater amounts of IL-1β after stimulation with LPS (lipopolysaccharides) compared to cells collected in the asymptomatic period and from healthy people [8 - 10]. Relapses of fever are accompanied by an increase in the number of neutrophils and monocytes and a decrease in the number of eosinophils and lymphocytes. Probably unknown environmental factors constitute a trigger mechanism to over-run the inflammatory response with activation of the complement and interleukins IL-1β/IL-18, with induction of Th1 response, followed by inhibition of the activated T lymphocytes in peripheral tissues. Long et al. hypothesized that the periodicity of the PFAPA syndrome derives from intermittent expression or suppression of antigens or epitopes of infectious agents or an alteration in the nature or kinetics of immunological response [11]. In spite of its strong familial clustering, the genetic basis and inheritance pattern of PFAFA are still unknown. Results of a relatively large cohort indicate that PFAPA syndrome is unlikely to be a monogenic condition [12]. Some variants of unknown significance in known auto-inflammatory-causing genes have been reported in PFAPA syndrome at higher frequency (also known as burden of variants). Best known examples include p.R121Q(R92Q) in TNF receptor superfamily member 1A (*TNFRSF1A*), heterozygosis or polymorphisms in the familial Mediterranean fever gene *MEFV*, mevalonate kinase *MVK* gene, or NLR family pyrin domain-containing 3 (*NLRP3*) [13].

In the literature, we found information about genetic similarities among PFAPA, recurrent aphthous stomatitis, and Behçet's disease. PFAPA shares risk loci at *IL12A*, *STAT4, IL10*, and *CCR1-CCR3* with Behçet's disease and recurrent aphthous stomatitis, defining a family of Behçet's spectrum disorders (BSDs). Manthiram and colleagues confirmed new class I and II *HLA* associations for PFAPA distinct from Behçet's disease and recurrent aphthous stomatitis, but HLA-B15 was identified as a risk allele for all of the BSDs [14]. All data suggest that PFAPA results from oligogenic or complex inheritance of variants in multiple disease genes and/or non-genetic factors. Because tonsillectomy is curative in most patients, there is a hypothesis that the palatine tonsils are the primary site of immune dysregulation in children with PFAPA. Tonsils of adult- and pediatric-onset in the asymptomatic PFAPA phase share unique histological features: smaller germinal center areas with a lower percentage of B lymphocytes, a higher percentage of CD8+ cytotoxic T lymphocytes and naïve T cells, and a lower percentage of CD4+ T cells with high expression of the inhibitory molecule PD-1 (programmed cell death 1) in germinal centers compared with controls [15 - 17]. In addition, high expression of T cell chemokines and proinflammatory cytokines in tonsils from patients with PFAPA was found [18].

CLINICAL MANIFESTATIONS

PFAPA is characterized by sudden onset of stereotypical episodes of fever, which persists for 3-6 days, resolves spontaneously, and regularly reoccurs every three to eight weeks; the average is approximately four weeks, alongside at least one of three main symptoms: aphthous stomatitis, cervical adenitis, and pharyngitis. It is an early-onset disease usually starting before the age of 5 years in 90% of patients [19]. The age of fever onset of adult patients with PFAPA is between 20 and 33 years of age. Fever episodes begin abruptly, and a temperature range from 38.5 to 41ºC for two to seven days and then abruptly fall to normal. Episodes rarely last for more than seven days. Thus, prolonged fever episodes should prompt consideration of other diagnoses. It is important to confirm that the symptoms with each episode are nearly identical. There is male predominance but no predilection for a particular ethnic group [3]. However, an increasing number of adults with PFAPA have been diagnosed in recent years [4, 5]. Aphthous stomatitis, usually on the inner lips or buccal mucosa, occasionally in the posterior pharynx, is present in about 40-70% of children reported with PFAPA. Patients have had few to several non-clustered, small (<5 mm), shallow ulcers that heal over 5 to 10 days. In opposite to the ulcers of Behçet syndrome, aphthous ulcers in PFAPA are not as large or painful nor do they scar. Prodromal symptoms such as malaise, irritability, and fatigue may manifest during the preceding days. Typically, along with a fever, tonsillitis is observed. Tonsils are red inflammatory exudates with different morphology (photo 1 and 2). Their appearance may

CHAPTER 13

Updates on Pediatric Hepatoblastoma

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Abstract: The developing human liver is embryologically central in embryogenesis. It plays a significant role as a hematopoietic and endocrine organ. During the development, hepatocytes change their phenotype. They vary from blueish cells to cells with an eosinophilic nuance and decreased nucleus to cytoplasm ratio. Apart from congenital abnormalities of this organ and inflammatory conditions that can populate medical charts in childhood and youth, the liver's neoplastic transformation in childhood and adolescence is a rare event. In children younger than three years, the liver's most dramatic neoplasm is represented by the occurrence of hepatoblastoma. It is an embryologic tumor. It retains the suffix "blastoma," similar to neuroblastoma as any other embryologic tumor. Hepatoblastoma originates presumably from the primitive embryo-fetal progenitors. In this chapter, we update our knowledge of this pediatric tumor, specifically the pathology and the treatment.

Keywords: Advocacy, Anatomy, Beckwith Wiedemann syndrome, Beta-Catenin, Child, Embryology, Familial adenomatous polyposis coli, Genetics, Hepatoblastoma, Liver, Microscopy, Neoplasm, Pathology, Quality Assurance, Radiology, Simpson–Golabi–Behmel syndrome, Sotos syndrome, Trisomy 18 syndrome, Tumor, World Health Organization.

INTRODUCTION

Hepatoblastoma is one of the most dramatic neoplasm of the first three years of life. It is an embryologic tumor of the liver showing several histologic patterns ranging from small round blue cell type morphology to a phenotype. It is quite similar to normal hepatocytes. The developing human liver is embryologically central in embryogenesis. It plays a major role as a hematopoietic and endocrine organ. In terms of development, hepatocytes change their phenotype. They vary

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from blueish cells to cells with an eosinophilic nuance and decreased or variable nucleus to cytoplasm ratio. Apart from congenital abnormalities of this organ and inflammatory conditions that can populate medical charts in childhood and youth, the liver's neoplastic transformation in childhood and adolescence is a rare event. About two-thirds of liver neoplasms occurring in the pediatric age are malignant. Nearly the same ratio is either hepatoblastoma or hepatocellular carcinoma. The former occurs mainly in the first triennium and the latter in children aged four or older [1 - 4]. This update will highlight the impressive increase in the overall survival of patients suffering from hepatoblastoma.

TUMOR CELL OF ORIGIN

In children younger than three years, the liver's most dramatic neoplasm is represented by the occurrence of hepatoblastoma. This tumor is an embryologic neoplasm. It retains the suffix “blastoma” similar to neuroblastoma or nephroblastoma (Wilms’ tumor) that characterizes most of the embryologic tumors [5]. Hepatoblastoma does not originate from primary hepatoblasts, but it seems that less differentiated cells are the culprit in this neoplastic event. The human fetal liver multipotent progenitor cells (hFLMPCs), which are poorly differentiated, can convert into various tissues. These tissues include hepatocytes, bone, fat, or bile ducts. The differences identified in multiple histological patterns of hepatoblastoma would explain its variety. In fact, up to 40% of tumor samples contain both epithelial and mesenchymal components [6]. The beta-catenin pathway is crucial for developing a variety of organs in the human body [7]. It is tightly linked to the Wnt signaling pathway. Wnt is a hybrid name created from the words Wingless and Int-1. In cell physiology, Wnt signaling use either cell-cell (paracrine) or same-cell communication (autocrine). It is so powerful that it is highly evolutionarily conserved in animals, ranging from fruit flies to humans. The canonical Wnt-beta-catenin pathway is a complex, evolutionarily conserved mechanism that regulates essential processes in both physiology and pathology. Among the several aspects, it has been demonstrated that Wnt-beta-catenin signalling controls embryogenesis, maturation and zonation [7]. In the healthy liver of a mature organism, the Wnt-beta-catenin pathway is mostly inactive. However, this pathway becomes active (or better re-active) during cell renewal and/or regenerative processes. These processes include several diseases, pre-malignant abnormalities, and neoplasms. In both hepatocellular carcinoma (HCC) and cholangiocarcinoma (CCA), which are the two most prevalent primary liver tumors in adults, Wnt-beta-catenin signaling is often hyperactivated. It is critical in promoting tumor cell growth and dissemination. Activating mutations have been found in a considerable percentage of both HCC and CCA, although HCC is largely dominant on CCA [8, 9]. Similarly, hepatoblastoma researchers discover Wnt-beta-catenin activation with beta-catenin mutations in most of these

embryologic tumors [10]. In a murine transgenic model using floxed beta-catenin (exons 2-6), and mice intercrossed with Albumin-Cre recombinase, Tan *et al*. found beta-catenin redundancy in the liver [11]. Lack of beta-catenin delays liver regeneration, but it does occur in a suboptimal way. In the case of 2/3 of partial hepatectomy, the Ctnnb1(loxp/loxp)-Alb-Cre(+/-) mice were passive in the first three days, but they showed an increase of hepatocyte proliferation after this time [11]. Beta-catenin has recently been demonstrated to cooperate with Yap signaling in the majority of hepatoblastomas [12 - 15].

CLINICAL PRESENTATION

Hepatoblastoma can occur sporadically or in the setting of familial cancer syndromes. These syndromes are Beckwith Wiedemann syndrome, Simpson–Golabi–Behmel syndrome, Sotos syndrome, familial adenomatous polyposis (FAP) coli, and trisomy 18 syndrome. Hepatoblastoma is more often seen in premature babies, with about 60% of a Japanese series affecting infants with birth weight less than 1000g [16]. In about 90% of patients with hepatoblastoma, there is an increase of alpha-fetoprotein (AFP), which may be puzzling because the premature liver contains and secretes a substantial amount of AFP. Other than nonspecific symptoms, including not gain of weight or weight loss associated with loss of appetite or anorexia, the abdominal mass can be discovered by ultrasound examination. It is a hyperechoic solid mass, which can be better delineated by computed tomography (CT) scan. CT scan will highlight the hepatoblastoma as a hypoattenuating mass with a clear boundary between the tumor and surrounding liver tissue.

PATHOLOGY

Hepatoblastoma can be essentially divided into two main categories, which include epithelial and epithelial/mesenchymal or mixed type. A few subtypes have been recognized in the epithelial category. They comprise fetal, embryonal, combined fetal and embryonal, macrotrabecular, and small cell types. The presence of mixed type is characterized by some mesenchymal tissue elements, such as cartilage or osteoid in addition to the epithelial component. In 6-8 weeks of gestation, the human liver shows basophilic cells with a high nucleus to cytoplasm ratio. This feature is seen in embryonal hepatoblastoma (EHB), which is the most often met histology pattern. These cells are approximately 10-15 micrometers in diameter and mostly round. The embryonal hepatoblast joins neighboring cells and grows in sheets. They form acinar (2D) or tubular (3D) structures around a central lumen. The more mature liver cells or fetal hepatoblasts acquire some features similar to more mature hepatocytes. These cells are relatively bigger than embryonal hepatoblasts. The nucleus to cytoplasm

CHAPTER 14

Updates on Mitochondrial Disorders in Children

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Abstract: Each human cell contains a few hundred mitochondria that are essential for aerobic energy metabolism. Among many fundamental metabolic pathways in mitochondria, the oxidative phosphorylation (OXPHOS) or the respiratory chain (RC) represents the final stage in oxidative metabolism. RC is under the dual control of the mitochondrial genome (mtDNA) and the nuclear genome (nDNA). The proper assembly and functioning of the RC involve many steps. The genetic defects in mtDNA, nDNA, and related functions of mitochondria affect the functioning of RC resulting in insufficient energy production and organ dysfunction.

Mitochondrial disorders are increasingly recognized. The clinical manifestations vary widely, causing a significant diagnostic challenge. Manifestations range from lesions of single tissue or structure to widespread lesions, including myopathies, encephalomyopathies, cardiopathies, neurogastrointestinal form, psychiatric symptoms, or complex multisystem syndromes. Coenzyme Q10 deficiency may present with isolated proximal muscle weakness. Leigh syndrome and MELAS are the most common clinical multisystem syndromes. The age at onset ranges from neonatal to adult life. The mortality remains high, and the median survival for early onset severe disease is 12years. Initial evaluations include blood transaminases, lactate-to-pyruvate ratio, amino acids, acylcarnitine profile, creatine kinase, and organic acids. Genetic tests are needed for confirmation.

Treatment depends on the specific mitochondrial disorder and its severity. In an acute presentation, an infection should be sought and treated promptly. Coenzyme Q10, thiamine, riboflavin, lipoic acid, L-carnitine, Creatine, and L-Arginine are found to be beneficial. Although there are no cures, treatments reduce symptoms or slow the decline in health.

Keywords: Arginine, Carnitine, Coenzyme Q, Encephalopathy, Energy, Lactic acidosis, Leigh syndrome, Magnetic resonance, MELAS, Mitochondrial disorders, Mitochondrial depletion, Mitochondrial membrane, mtDNA, Muscle

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biopsy, Myopathy, nDNA, Neuropathy, OXPHOS, Ragged-red fibers, Respiratory chain, Riboflavin, Stroke, Thiamine.

INTRODUCTION

Mitochondria are the cellular organelles responsible for oxidative phosphorylation (OXPHOS) and the production of energy in the form of adenosine triphosphate (ATP). The energy production occurs in the mitochondrial respiratory chain (RC). Mitochondria also perform other tasks such as combating the production of reactive oxygen species and initiating apoptosis. They also house a variety of metabolic reactions such as pyruvate oxidation and metabolism of amino acids, fatty acids, and steroids. The five complexes, complexes I to V, of the mitochondrial RC contain approximately 80 proteins, of which 13 are encoded by mtDNA and the remaining proteins by the nDNA. The nDNA ultimately controls the proper assembly and functioning of the RC involving many steps. The defects of mtDNA and nDNA result in two important categories of mitochondrial disorders. Mutations in mtDNA such as tRNA or rRNA gene mutations and rearrangements may impair the total mitochondrial protein synthesis or may affect one of the 13 respiratory chain subunits encoded by mtDNA [1 - 4].

Mitochondrial disorders are inherited disorders of energy metabolism caused by impairment of the OXPHOS system. Defects in any of the mitochondrial functions can lead to primary mitochondrial disorders. Mitochondrial disorders present with a wide range of clinical expressions. Multisystem involvement is the hallmark of the disorder and is quite disabling. The organ systems that mostly rely on aerobic metabolism are preferentially affected. In patients with predominantly multisystem disorder, there is a variable combination of central and/or peripheral nervous system involvement, ophthalmologic abnormalities, sensorineural hearing loss, gastrointestinal symptoms, cardiac, hepatic and renal disorder, endocrine dysfunction, and short stature. Central nervous system involvement is also common. Single structure involvement may be seen in Leber's hereditary optic neuropathy (LHON) and maternally inherited non-syndromic deafness. Mitochondrial myopathy refers to skeletal muscle involvement either alone or with central nervous system disorder. The major mitochondrial depletion syndromes (MDS) include myopathic (mutations in TK2, RRM2B, and AGK), encephalomyopathic (mutations in SUCLA2, SUCLG1, and RRM2B), hepatocerebral (mutations in GDUOK, MPV17, POLG, and C10ORF2), and/or neurogastrointestinal (TYMP mutations) types. The age of onset of mitochondrial disorders varies from neonatal to adult life. Neonates, too, have severe manifestations. The diagnosis, lab investigation, and treatment depend on the clinical type and severity of the disorder [1, 2, 5, 6].

EPIDEMIOLOGY

The current prevalence of childhood-onset mitochondrial disorders has been predicted to range from 5 to 15 cases per 10,000. Primary genetic mitochondrial disorders are among the most common inborn errors of metabolism, with a minimum incidence of 1: 5,000. The point prevalence in children younger than age 16 years is estimated to be 1 in 21,000. A population-based study from western Sweden from 1984 until 1999 found that the incidence of mitochondrial encephalomyopathies in preschool aged children was 1 in 11,000 [7]. The incidence and prevalence of mitochondrial myopathies are slightly less than those reported for mitochondrial encephalomyopathies. The prevalence of mtDNA point mutations was greater than 1 in 200 individuals among newborns. Due to variable heteroplasmy, some of these mutations will never be clinically expressed. An Australian study estimated the minimal birth prevalence of primary mitochondrial disorders to be 6.2 cases per 100,000 births [8]. The mortality of these disorders in childhood is high, and many children are expected to survive till 3 to 9 years of age. The median survival for children with infantile onset is said to be 12years.

PATHOGENESIS

Mitochondria, the organelles present in each human cell, carry out many fundamental metabolic pathways, including the respiratory chain, fatty acid β-oxidation, and the tricarboxylic acid (TCA) cycle. The much essential aerobic energy metabolism takes place in the mitochondria. The oxidative phosphorylation or the respiratory chain represents the final stage in oxidative metabolism. The respiratory chain is located in the inner mitochondrial membrane and is composed of five intramembrane complexes and two mobile electron carriers, coenzyme Q10 (CoQ10) and cytochrome c. The five multi-subunit enzyme complexes include complex I, or NADH ubiquinone reductase, which re-oxidizes NADH derived from the oxidation of fatty acids, amino acids, and pyruvate; complex II, or succinate-ubiquinone oxidoreductase, which oxidizes FADH2 derived from the TCA cycle; complex III, or ubiquinol-ferricytochrome-c oxidoreductase; complex IV or cytochrome c oxidase, and complex V, or ATP synthase. Complexes I, III, and IV pump protons from the mitochondrial matrix into the intermembrane space and the energy which this creates is harnessed by ATP synthase for the production of ATP from ADP. Both the mitochondrial and nuclear genes contribute proteins to the OXPHOS pathway. Human mtDNA is a 16.569-kb circular, double-stranded molecule, which contains 37 genes: 2 rRNA genes, 22 tRNA genes, and 13 structural genes encoding the respiratory chain subunits. About 13 proteins of RC are encoded by mtDNA, and the remaining proteins by the nDNA. Complex II, coenzyme Q, and cytochrome c are exclusively encoded by nDNA [3, 4].

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